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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of	:	Examiner: Shin Lin Chen
Bernadino Ghetti et al.	:	Group Art Unit: 1632
Serial No. ~~10/684,742~~ 10/684,142	:	File Ref: 1857-IURTC.0253US
Filed: October 14, 2003	:	
For: "FERRITIN LIGHT SUBUNIT VARIANT-ENCODING NUCLEIC ACIDS, POLYPEPTIDES, TRANSGENIC ANIMALS COMPRISING THE SAME, ANTIBODIES THERETO, AND METHODS OF USE THEREOF"	:	

DECLARATION OF DR. VIDAL UNDER 37 C.F.R. §1.132

I, Ruben Vidal, hereby declare that:

1. I am a citizen of the United States and reside at 3747 Power Dr., Carmel, IN 46033.

2. I received a Ph.D. degree in Biological Sciences in 1992 from the National University at Rosario, Argentina. Additional details of my education and professional history are set forth in my curriculum vitae, attached hereto as Exhibit A.

3. I have over 16 years experience in the field of neuroscience research, my particular area of expertise being in neurodegenerative disorders.

4. I am the author or co-author of more than 35 peer reviewed scientific articles on the subjects of neuroscience and human disease. A list of these articles

is set forth in my curriculum vitae, attached hereto.

5. I currently hold the position of Associate Professor in the Department of Pathology and Laboratory Medicine and senior scientist at the Stark Neurosciences Research Institute and Indiana Alzheimer Disease Center at Indiana University School of Medicine, Indianapolis, Indiana.

6. I am a co-inventor, along with Bernardino Ghetti, of the subject matter described and claimed in U.S. Patent Application 10/684,742 (hereinafter the '742 application).

7. I have read and am familiar with the Official Action dated August 14, 2006, in the present application. I understand that the Examiner has rejected claims 17-21, 25, 26 and 28 for lack of utility, contending that the specification provides general assertions and has not provided any suggestion of a correlation between any phenotype of the claimed transgenic animals, the altered ferritin light chain gene, and a disease or disorder. The Examiner has also rejected claims 17-21, 25, 26 and 28 for lacking sufficient enablement asserting that adequate guidance for making and using the claimed transgenic animals comprising an altered FTL gene is not provided. The Examiner erroneously asserts that because no phenotype is disclosed, a skilled artisan would have to engage in undue experimentation to practice the full scope of the invention. Lastly, the Examiner has rejected claims 17-20 and 26 contending the subject matter of these claims is not described in a way which indicates that we were in possession of the transgenic mice of the invention. The

purpose of this declaration is to provide factual evidence that the claimed transgenic animals can be generated by the methods provided in the '742 application and I respectfully disagree with the Examiner for the reasons set forth in the following paragraphs.

STATEMENTS RELATING TO THE UTILITY OF CLAIMS 17-21, 25, 26 AND 28

8. The specification of the '742 application provides a description of the disorder "hereditary ferritinopathy" in Example I, page 55. This neurodegenerative disease is associated with a genetic defect in the coding region of the ferritin light chain (FTL) gene (characterized by a 'TC' insertion following nucleotide 498) which results in intranuclear and intracytoplasmic depositions of ferritin in glia and subsets of neurons in the central nervous system. The disorder is associated with tremors, behavioral disturbances and cognitive dysfunction. (See specification page 56, lines 15-27).

9. The data attached to this declaration clearly demonstrate that mice with an altered FTL gene (TC insertion after nucleotide 498), generated using the techniques described in the present application, have the biological phenotype described above. The data show that intranuclear and intracytoplasmic ferritin deposits were observed in brain tissue of FTL transgenic mice. See Exhibit D. Specifically, the data reveal that transgenic mice carrying the FTL 498InsTC mutation under control of the mouse prion protein gene promoter correlates with the phenotype observed in hereditary ferritinopathy. Moreover,

the transgenic mice showed behavioral and motor deficits such as inability to spread hind limbs upon tail elevation, lack of grooming, and inability to grip a wire cage. Considering the phenotype of the claimed transgenic animal and the correlation between the phenotype of the mouse and the disease hereditary ferritinopathy, the utility of the claimed transgenic animal has been established. For example, one utility described in the specification at page 38 teaches that the claimed transgenic mice provide a model system for the study of neurodegeneration associated with ferritin accumulation. Such mice also provide a useful *in vivo* model for studying agents that may have efficacy for the treatment of ferritinopathies as disclosed at page 42, line 34 through page 43, line 5. This use provides a clear and credible utility for the transgenic mice of the invention which would be apparent to the skilled artisan.

STATEMENTS REGARDING POSSESSION OF THE INVENTION AND ADEQUACY OF THE DISCLOSURE TO ENABLE PRACTICE OF THE INVENTION

10. The present application fully enables the invention claimed in claims 17-21, 25, 26 and 28. In fact, transgenic animals comprising an altered ferritin light chain operably linked to the mouse MoPrP prion promoter have been generated as contemplated and claimed in claims 17-21.

As exemplified in the specification, I have generated a transgenic animal with a 'TC' insertion following nucleotide 498 of the FTL gene. The specification of the '782 application discloses methods of introducing transgenes in laboratory mice, and the FTL variant

transgenic mice were generated using similar techniques as those disclosed at page 38, line 10, over to page 41, line 23. To generate expression constructs suitable for introduction into an animal, the FTL498-499InsTC mutant FTL sequence was cloned by RT-PCR from RNA isolated from brain tissue using oligonucleotide primers containing an XhoI site, a Kozack consensus sequence, and a stop codon, and the 5'-UTR containing the IRE sequence was excluded from the construct. The FTL498-499InsTC cDNA was inserted into the pBS/MoPoP.Xho vector. This vector was described in Borchelt et al. (Genet. Anal. (1996) 13(6):159-163) and is readily available to the skilled artisan. The orientation of the cDNA was then verified by sequencing.

The resulting construct was linearized and gel-purified prior to injection into hybrid C3HeB/FeJ mouse embryos. Transgenic lines were established using standard methods at the Indiana University Transgenic and Knock-out Mouse Core Facility. The transgenic lines were maintained by crossing transgenic animals to non-transgenic C57BL/6J mice.

DNA was extracted by proteinase K digestion from the transgenic animal tail clips followed by ethanol precipitation. The transgene was detected by PCR amplification of a 533 bp product using a forward primer (FTLfE1: 5'-AACAGCCTGGTCAATTTGT-3') and a reverse primer (FTLRE4: 5'-AAGCCCTATTACTTTGCAAGGGG-3') located in the FTL cDNA sequence.

Presence of the transgene was assessed by PCR amplification using the forward and reverse primers described in the preceding paragraph. See Exhibit B for analysis of four transgenic mice and one control mouse demonstrating the presence of the FTL transgene.

As shown in Exhibit C, protein levels of the FTL variant in the different founder lines (Mut 1-4) was assessed by western blot. The transgene was detected using antibody 1283, which is specific for the FTL variant and was described in Vidal et al. (J. Neuropathol. Exp. Neurol. (2004) 63:363-380). Additionally, Exhibit C also shows expression of the FTL variant in the brain and other organs of one of the transgenic mice.

Attached as Exhibit D are figures demonstrating ferritin inclusions in different brain areas. Specifically, immunohistochemistry shows intranuclear and intracytoplasmic ferritin in the cerebellum and brain stem from a 4 month transgenic mouse (Mut-4) that was detected using the mutant FTL antibody 1283, and an antibody that recognizes both the wild type and mutant FTL genes (Dako Inc.). Ferritin deposits are labeled in brown.

The data described above clearly demonstrates the successful introduction of the FTL variant into an animal and the aberrant phenotype resulting from the same.

11. The Examiner has issued various objections and rejections with respect to the present invention on the grounds that a skilled artisan would have to engage in undue experimentation to practice over the full scope of the invention in view of the inherent unpredictability of the resulting phenotypes of transgenic animals. In order to sustain these rejections, the Examiner generally maintains that production of transgenic animals is an unpredictable art. As indicated in the foregoing paragraph, generation of the transgenic mice of the present claims was fairly straightforward and in no way required "undue experimentation." It is my opinion that the state

of the art of transgenic animals does not reach the extreme unpredictability asserted by the Examiner. Indeed, the experimental results set forth in Exhibits B-D herein demonstrate generation of transgenic animals comprising an altered ferritin light chain gene along with the described phenotype of the transgenic animals using the methodology provided in the specification as filed.

12. Inasmuch as the specification of the '742 application discloses constructs and methods to generate strains of laboratory mice carrying the FTL variant of the invention (See specification p.38, line 3 through p.42, line 33), and Exhibits B-D demonstrate the successful production of the same, we submit that the present application fully enables the invention claimed in claims 17-21, 25, 26 and 28.

THE SPECIFICATION DOES PROVIDE A CLEAR WRITTEN DESCRIPTION OF THE INVENTION ENCOMPASSED BY CLAIMS 17-20 and 26

13. The Examiner has rejected the present application for failing to comply with the written description requirement since it allegedly contains subject matter not described in such a way as to reasonably convey that we had possession of the claimed invention.

14. As the '742 application and the results in Exhibits B-D indicate, delivery of an altered FTL gene, SEQ ID No. 1, under the control of the mouse prion protein gene promoter (described at page 37, lines 1-5) into a mouse results in the expression of the variant FTL molecules that accumulate in glia and neurons. These experimental results

clearly demonstrate the operability of my invention and further show that we were in possession of the invention at the time our application was filed.

15. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so make are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the above-referenced application or any patent issued thereon.

11/16/06
DATE

Dr. Ruben Vidal

10/31/06

CURRICULUM VITAE

NAME: Ruben Vidal

Current Appointment and Address: Associate Professor
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Date and Place of birth: 05/25/1963 Rosario, Argentina
Citizenship: USA

EDUCATION:

Undergraduate/Graduate:

1989 M.S. National University at Rosario, Argentina. (Clinical Laboratories)

1992 Ph.D. National University at Rosario, Argentina. "Hereditary Cerebral Hemorrhage with Amyloidosis, Dutch Type. Cloning and sequence of the Alzheimer's disease gene that encodes the Amyloid Precursor Protein of the amyloid deposited in cerebral vessel walls."
Thesis Advisor: Blas Frangione, M.D., Ph.D., Department of Pathology, New York University School of Medicine, New York, NY

Postdoctoral Training:

1992-1994 Department of Dermatology, New York University School of Medicine, New York, NY

1995-1996 Department of Pathology, New York University School of Medicine, New York, NY

ACADEMIC APPOINTMENTS:

1985-1989 Teaching Assistant, Biology I/II, Department of Biology, National University at Rosario, Argentina

1989-1990 Instructor in Immunology, Department of Pathology, National University at Rosario, Argentina

1990-1992 Assistant Researcher, Department of Pathology, New York University School of Medicine, New York, NY

1992-1994 Post-Doctoral Fellow, Department of Dermatology, New York University School of Medicine, New York, NY

1995-2000 Assistant Researcher, Department of Pathology, New York University School of Medicine, New York, NY

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1996-2000	Instructor in Pathology, Department of Pathology, New York University School of Medicine, New York, NY
2000	Research Assistant Professor, Department of Pathology, New York University School of Medicine, New York, NY
2000-2006	Assistant Professor, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN
2000-present	Primary investigator. Indiana Alzheimer Disease Center. Indiana University School of Medicine, Indianapolis, IN
2006-present	Associate Professor (with tenure), Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN
2006-present	Primary investigator. Stark Neurosciences Research Institute. Indiana University School of Medicine, Indianapolis, IN

MEMBERSHIP IN PROFESSIONAL ORGANIZATIONS:

1998-present	Society for Neuroscience
2001-present	American Association of Neuropathologists
2004-present	Japanese Association of Neuropathologists

HONORS AND AWARDS:

1994	Neostrata Research Award. Dermatology Foundation
2000	Traveling award. Alzheimer's Association, Pivotal Research Program-World Alzheimer Congress 2000
2001	Moore Award. American Association of Neuropathologists
2003	Guest of Honor. Department of Clinical Medicine. National University of La Plata School of Medicine, Argentina

PROFESSIONAL SERVICE:

Scientific Journal Reviewer:

Proceedings of the National Academy of Sciences of the United States of America, Journal of Neuropathology and Experimental Neurology, Amyloid, Trends in Biochemical Sciences, Annals of Neurology, The Journal of the Neurological Sciences, Neurology, Gene Reviews, Progress in Neurobiology, BBB-Molecular Basis of Disease.

Scientific Journal Board:

2005-present	Journal of Neuropathology and Experimental Neurology

Grant Reviewer:

1998-2001	Member of the Review Board. Agencia Nacional de Promocion Cientifica y Tecnologica. Secretaria de Ciencia y Tecnica. Ministerio de Cultura y Educación, Argentina.
2000-present	Member of the Initial Review Board of the Medical and Scientific Advisory Council. Alzheimer's Association, USA.

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2005-present Grant reviewer. Telethon Grants Program, Italy.

2006-present Grant reviewer. American Federation for Aging Research (AFAR), USA.

2006-present Consultant. Cell Death and Injury in Neurodegeneration Study Section (CDIN). NIH, USA.

Service to patients/clients and related clinical institutions:

2000-present Genetic analysis and biochemical studies of individuals affected by neurodegenerative diseases. Indiana Alzheimer Disease Center. Indiana University School of Medicine, Indianapolis, IN, USA.

UNIVERSITY SERVICE:

2001-present Faculty member. Medical Student Mentoring Program. Indiana University School of Medicine

2004-present Faculty member. Teacher Learner Advocacy Committee. Indiana University School of Medicine.

2005-present Regular Member of the Institutional Biosafety Committee (IBC). Indiana University School of Medicine.

INVITED SEMINARS:

2000 New York University School of Medicine. Department of Pathology. Skirball Institute. New York, N.Y. "Mutations in the *BRI* gene on chromosome 13 cause Alzheimer's type of dementia"

2000 Indiana University School of Medicine. Department of Pathology. Indianapolis, IN. "Familial British and Danish dementias"

2001 Indiana University School of Medicine. Department of Psychiatry. Institute of Psychiatric Research. Indianapolis, IN. "Chromosome 13-related Dementias"

2002 Indiana University School of Medicine. Department of Biochemistry and Molecular Biology. Indianapolis, IN. "Amyloid and Chromosome 13 Related Dementias"

2002 Indiana University School of Medicine. Indiana Alzheimer Disease Center. External Advisory meeting. Indianapolis, IN. "CNS and systemic deposition of ferritin and iron associated with a novel autosomal dominant neurodegenerative disease"

2002 Beckman Coulter. Advanced Technology Seminar Series. Tools and Techniques for Systems Biology. Pittsburgh, P.A. "Deciphering Presenile Dementia"

2002 Indiana University School of Medicine. Department of Medical Genetics. Indianapolis, IN. "Chromosome 13 dementia syndrome"

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2002 Indiana University School of Medicine. Department of Pathology and Laboratory Medicine. Gregory Derringer Pathology Grand Rounds. "Sporadic and familial cerebral amyloid angiopathies"

2002 Symposium of the Society for Experimental Neuropathology. New York, N.Y. "Hereditary ferritinopathy"

2003 National University of La Plata School of Medicine. Department of Clinical Medicine. La Plata, Argentina. "Immunoglobulins and Amyloid"

2003 XVth International Congress of Neuropathology. Plenary Lecture. Torino, Italy. "Neurodegenerative diseases caused by the deposition of proteins with an abnormal carboxy terminus"

2005 Louisiana State University School of Medicine. Neuroscience Center of Excellence. New Orleans, LA. "Hereditary Ferritinopathy"

2006 Indiana University School of Medicine. Department of Medical Genetics. Indianapolis, IN. "Hereditary Ferritinopathy: A new neurodegenerative disease associated with abnormal protein deposition"

2006 Indiana University School of Medicine. Department of Pathology and Laboratory Medicine's Centennial Celebration. "Neurodegenerative diseases caused by the deposition of proteins with an abnormal carboxyl-terminus".

PRINT AND ELECTRONIC PUBLICATIONS:

1. J. Ghiso, T. Wisniewski, **R. Vidal**, A. Rostagno, and B. Frangione. Epitope map of two polyclonal antibodies that recognize amyloid lesions in patients with Alzheimer's disease. (1992) *Biochem. J.* 282:517-522.

2. **R. Vidal**, J. Ghiso, G. Gallo, M. Cohen, P.-L Gambetti, and B. Frangione. Amyloidoma of the CNS. II. Immunohistochemical and biochemical study. (1992) *Neurology* 42:2024-2028.

3. **R. Vidal**, I. Fernandez-Madrid, B. Frangione, and E. Levy. Sequencing of the Alzheimer's APP gene Dutch Variant (APP-D). (1993) *Hum. Mutat.* 2:495.

4. T. Magnaldo, **R. Vidal**, M. Ohtsuki, I. Freedberg, and M. Blumenberg. On the role of AP2 in epithelial-specific gene expression. (1993) *Gene Expr.* 3:307-315.

5. **R. Vidal**, F. Garzuly, H. Budka, M. Lalowski, R. Linke, F. Britting, B. Frangione, and T. Wisniewski. Meningocerebrovascular Amyloidosis Associated with a Novel Transthyretin (TTR) Missense Mutation at Codon 18 (TTRD18G). (1996) *Am. J. Pathol.* 148:361-366. (**Article Featured on Cover. Editorial**).

6. F. Garzuly, **R. Vidal**, T. Wisniewski, F. Britting, and H. Budka. Familial meningo-cerebrovascular amyloidosis, Hungarian type, with mutant transthyretin (TTRAsp18Gly). (1996) *Neurology* 47:1562-1567.

7. G. Gallo, F. Goñi, F. Boctor, **R. Vidal**, A. Kumar, B. Frangione, and J. Ghiso. Light chain cardiomyopathy: Immunohistochemical and biochemical analysis of the

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light chain deposits. (1996) *Am. J. Pathol.* 148:1397-1406. (**Article Featured on Cover. Editorial**).

8. F. Perini, **R. Vidal**, B. Ghetti, F. Tagliavini, B. Frangione, and F. Prelli. PrP27-30 is a normal soluble Prion protein fragment released by human platelets. (1996) *Biochem. Biophys. Res. Comm.* 223:572-577.

9. **R. Vidal**, J. Ghiso, T. Wisniewski, and B. Frangione. Alzheimer's Presenilin 1 gene expression in platelets and megakaryocytes. Identification of a novel splice variant. (1996) *FEBS Lett.* 393:19-23.

10. A.Rostagno, **R. Vidal**, A. Kumar, J. Chuba, G. Niederman, L. Gold, B. Frangione, J. Ghiso,and G. Gallo. Fibrillary Glomerulonephritis related to serum fibrillar immunoglobulin-fibronectin complexes. (1996) *Am. J. Kidney Dis.* 28:676-684. (**Article Featured on Cover. Editorial**).

11. **R. Vidal**, B. Kaplan, A. Kumar, J. Ghiso, B. Frangione, and G. Gallo. Amino-terminal identity of co-existent amyloid and nonamyloid immunoglobulin kappa light chain deposits. A human model to study alterations of protein conformation. (1997) *Clin. Exp. Immunol.* 110:464-471.

12. C. Decourt, G. Touchard, J.L. Preud'homme, **R. Vidal**, H. Beaufils, M.C. Diemert, and M. Cogné. Complete primary sequence of two λ immunoglobulin light chains in myelomas with non-amyloid (Randall type) light chain deposition disease. (1998) *Am. J. Pathol.* 153:313-318.

13. A. Jimenez-Huete, P. M. J. Lievens, **R. Vidal**, P. Piccardo, B. Ghetti, F. Tagliavini, B. Frangione, and F. Prelli. Endogenous proteolytic cleavage of normal and disease-associated isoforms of the human prion protein in neural and non-neural tissues. (1998) *Am. J. Pathol.* 153:1561-1572.

14. M. Pizzolato, G. Bragantini, P. Bresciani, S. Pavlovski, J. Chuba, **R. Vidal**, A. Rostagno, and J. Ghiso. IgG1-κ biclonal gammopathy associated with multiple myeloma suggests a regulatory mechanism. (1998) *Br. J. Haematol.* 102:503-508.

15. B. Kaplan, **R. Vidal**, A. Kumar, J. Ghiso, and G. Gallo. Immunochemical microanalysis of amyloid proteins in fine-needle aspirates of abdominal fat. (1999) *Am. J. Clin. Pathol.* 112:403-407.

16. S. Derét, L. Denoroy, M. Lamarine, **R. Vidal**, B. Mougenot, B. Frangione, F. Stevens, P.M. Ronco, and P. Aucouturier. Kappa light chain-associated Fanconi's syndrome: Molecular analysis of monoclonal immunoglobulin light chains from patients with and without intracellular crystals. (1999) *Protein Eng.* 12:363-369.

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17. **R. Vidal**, F. Goñi, F. Stevens, P. Aucouturier, A. Kumar, B. Frangione, J. Ghiso, and G. Gallo. Somatic mutations of the L12a gene in V-κI light chain deposition disease: Potential effects on aberrant protein conformation and deposition. (1999) *Am. J. Pathol.* 155:2009-2018.

18. A. Rostagno, **R. Vidal**, B. Kaplan, J. Chuba, A. Kumar, J. Elliot, B. Frangione, G. Gallo, and J. Ghiso. pH-dependent fibrillogenesis of a VκIII Bence Jones protein. (1999) *Br. J. Haematol.* 107:835-843.

19. **R. Vidal**, B. Frangione, A. Rostagno, S. Mead, T. Revesz, G. Plant, and J. Ghiso. A stop-codon mutation in the *BRI* gene associated with familial British dementia. (1999) *Nature* 399:776-781.

20. V. Askanas, W. King Engel, R. B. Alvarez, B. Frangione, J. Ghiso, and **R. Vidal**. Inclusion-body myositis accompanied by muscle blood-vessel and cardiac amyloidosis in a black patient homozygous for the transthyretin Val122Ile allele. (2000) *Ann. Neurol.* 47:544-549.

21. **R. Vidal**, T. Révész, A. Rostagno, E. Kim, J. L. Holton, T. Bek, M. Bojsen-Møller, H. Braendgaard, G. Plant, J. Ghiso and B. Frangione. A decamer duplication in the 3' region of the *BRI* gene originates an amyloid peptide that is associated with dementia in a Danish kindred. (2000) *Proc. Natl. Acad. Sci. U. S. A.* 97: 4920-4925.

22. T. Tokuda, M. Calero, E. Matsubara, **R. Vidal**, A. Kumar, B. Permanne, B. Zlokovic, J. Smith, M. J. LaDu, A. Rostagno, B. Frangione, and J. Ghiso. Lipidation of Apolipoprotein E influences its isoform specific interaction with Alzheimer's amyloid β-peptides. (2000) *Biochem. J.* 348:359-365.

23. **R. Vidal**, M. Calero, P. Piccardo, M. R. Farlow, F.W. Unverzagt, E. Méndez, A.Jiménez-Huete, R. Beavis, G. Gallo, E. Gomez-Tortosa, J. Ghiso, B. T. Hyman, B. Frangione, and B. Ghetti. Senile dementia associated with Aß angiopathy and tau perivascular pathology but not neuritic plaques in patients homozygous for the *APOE*-ε4 allele. (2000) *Acta Neuropathol.* 100:1-12.

24. J. L. Holton, J. Ghiso, T. Lashley, A. Rostagno, C. J. Guerin, G. Gibb, H. Houlden, H. Ayling, L. Martinian, B. H. Anderton, N. W. Wood, **R. Vidal**, G. Plant, B. Frangione, T. Revesz. Regional distribution of ABri deposition and its association with neurofibrillary degeneration in familial British dementia. (2001) *Am.J. Pathol.* 158:515-526.

25. M-H.Teng, J-Y Yin, **R. Vidal**, J. Ghiso, A. Kumar, R. Rabenou, A. Shah, D. Jacobson, C. Tagoe, G. Gallo, and J. Buxbaum. Amyloid and non-fibrillar deposits in mice transgenic for wild-type human transthyretin: A possible model for senile systemic amyloidosis. (2001) *Lab. Invest.* 81:385-396. **(Article Featured on Cover. Editorial)**.

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26. **R. Vidal**, M. Calero T. Révész, G. Plant, J. Ghiso and B. Frangione. Sequence, genomic structure and tissue expression of Human *BRI3*, a member of the *BRI* gene family. (2001) *Gene.* 266:95-102.

27. J. Ghiso, J. Holton, L. Miravalle , M. Calero, T. Lashley, **R.Vidal**, H. Houlden, N. Wood, T. A. Neubert, A. Rostagno, G. Plant, T. Révész, and B. Frangione. Systemic amyloid deposits in familial British dementia. (2001) *J. Biol. Chem.* 276:43909-43914.

28. B. Poeggeler, L. Miravalle, M. G. Zagorski, T. Wisniewski, Y. J. Chyan, Y. Zhang, H. Shao, T. Bryant-Thomas, **R. Vidal**, B. Frangione, J. Ghiso, and M. A. Pappolla. Melatonin reverses the profibrillogenic activity of apolipoprotein E4 on the Alzheimer amyloid Aβ Peptide. (2001) *Biochemistry* 40:14995-5001.

29. J. L. Holton, T. Lashley, J. Ghiso, H. Braendgaard, **R. Vidal**, C. Guerin, G. Gibb, D. P. Hanger, A. Rostagno, B. H. Anderton, C. Strand, H. Ayling, G. Plant, B. Frangione, M. Bojsen-Møller, and T. Revesz. Familial Danish dementia: A novel form of cerebral amyloidosis associated with deposition of both amyloid-Dan and amyloid-beta. (2002) *J. Neuropathol. Exp. Neurol.* 61(3):254-267.

30. **R. Vidal**, M. B. Delisle, O. Rascol, and B. Ghetti. Hereditary ferritinopathy. (2003) *J. Neurol. Sci.* 207:110-111.

31. A. Roher, T. Kokjohn, C. Esh, N. Weiss, J. Childress, W. Kalback, D. C. Luehrs, J. Lopez, D. Brune, Y.-M. Kuo, M. Farlow, J. Murrell, **R. Vidal**, and B. Ghetti. The human amyloid-beta precursor protein$_{770}$ mutation 717 Val→Phe generates peptides longer than Aβ_{42} and flocculent amyloid aggregates. (2004) *J. Biol. Chem.* 279:5829-5836.

32. S.-I. Choi, **R. Vidal**, B. Frangione, and E. Levy. Axonal transport of British and Danish amyloid peptides via secretory vesicles. (2004) *FASEB J.* 18:373-5.

33. B. Azzarelli, L. Miravalle, and **R. Vidal**. Polyclonal antibodies raised against the Oligodendrocyte Transcription Factor 1 (Olig1) recognize neoplastic oligodendrocytes. (2004) *J. Neuropathol. Exp. Neurol.* 63:170-179.

34. **R. Vidal**, B. Ghetti, M. Takao, C. Brefel-Courbon, E. Uro-Coste, B.S. Glazier, V. Siani, M.D. Benson, P. Calvas, L. Miravalle, O. Rascol, and M.B. Delisle. Intracellular ferritin accumulation in neural and extraneural tissue characterizes a neurodegenerative disease associated with a mutation in the *Ferritin Light Polypeptide* gene. (2004) *J. Neuropathol. Exp. Neurol.* 63:363-80.

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35. M. Takao, B. Ghetti, H. Yoshida, P. Piccardo, Y. Narain, J. R. Murrell, **R. Vidal**, B. S. Glazier, R. Jakes, M. Tsutsui, M. G. Spillantini, R. A. Crowther, M. Goedert, and A. Koto. Early-onset dementia with Lewy bodies. (2004) *Brain Pathol.* 14:137-147.

36. L. Miravalle, M. Calero, M. Takao, A. E. Roher, B. Ghetti, and **R. Vidal**. Amino-terminally truncated Aβ peptide species are the main component of cotton wool plaques. (2005) *Biochemistry.* 44:10810-10821.

37. T. Foroud, N. Pankratz, A. P. Batchman, M. W. Pauciulo, **R. Vidal**, L. Miravalle, H. H. Goebel, L. J. Cushman, B. Azzarelli, H. Horak, M. Farlow, and W. C. Nichols. A mutation in myotilin causes spheroid body myopathy. (2005) *Neurology.* 65:1936-1940.

Chapters in books and reviews:

1. J. Ghiso, **R. Vidal**, G. Gallo and B. Frangione. Amyloidosis. (1995) Braz. J. Rheumatol. 35:93-102.

2. B. Frangione, E. Castaño, T. Wisniewski, J. Ghiso, F. Prelli and **R. Vidal**. Apolipoprotein E and Amyloidogenesis. In: The nature and origin of amyloid fibrils. (1996) Wiley, Chichester. Ciba Found. Symp. 199:132-145.

3. G. Gallo, P. Lazowski, A. Kumar, **R. Vidal**, D. Baldwin, J. Buxbaum. Renal and Cardiac Manifestations of B-cell dyscrasias with nonamyloidotic monoclonal light chain and light and heavy chain deposition disease. In: Advances in Nephrology From the Necker Hospital.(1998) Edited by J. P. Grünfeld, J. F. Bach, H. Kreis, D. Broneer, and M. H. Maxwell. 28: 355-382.

4. **R Vidal**, X. Shao, J. Ghiso, P. Gorevic and B. Frangione. Biotechnological production of Aβ peptides. (1999) In: Alzheimer's disease and related disorders: Etiology, Pathogenesis and Therapeutics. Edited by K. Iqbal, D. F. Swaab, B. Winblad, and H. M. Wisniewski. 723-728.

5. J. Ghiso, **R. Vidal**, A. Rostagno, S. Mead, T. Revesz, G. Plant and B. Frangione. A newly formed amyloidogenic fragment due to stop codon mutation causes familial British dementia. (2000) *Ann. N. Y. Acad. Sci.* 903:129-137.

6. B. Frangione, **R. Vidal**, A. Rostagno and J. Ghiso. Familial cerebral amyloid angiopathies and dementia. (2000) *Alzheimer Dis. Assoc. Disord.* **14** Suppl.1:S25-30.

7. B. Ghetti, P. Piccardo, B. Frangione, **R. Vidal**, J. Ghiso. Neuropathology and Genetics of CAA-Prion protein and Familial British dementia. (2000) In: Cerebral amyloid angiopathy in Alzheimer's disease and related disorders. Edited by M. Verbeek, R. M. W. de Waal and H. V. Vinters. 237-247.

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8. **R. Vidal**, J. Ghiso and B. Frangione. Amiloidosis. Mecanismos de formación y depósito de fibras amiloide. (2000) In: Reumatología. Edited by J. A. Maldonado Cocco, G. Citera and S. O. Paira. 702-712. (In Spanish).

9. **R. Vidal**, J. Ghiso, and B. Frangione. New familial forms of cerebral amyloid and dementia. (2000) *Mol. Psychiatry* 5(6):575-576. (Invited review)

10. J. Ghiso, **R. Vidal**, A. Rostagno, L. Miravalle, J. L. Holton, T. Revesz, G. Plant and B. Frangione. Amyloidogenesis in familial British dementia is associated with a genetic defect on chromosome 13. (2000) *Ann. N. Y. Acad. Sci.* 920:84-92.

11. **R. Vidal**, T. Révész, A. Rostagno, T. Bek, H. Braendgaard, G. Plant, J. Ghiso, and B. Frangione. A decamer duplication in the *BRI* gene originates a de-novo amyloid peptide that causes dementia in a Danish kindred. (2001) In: Alzheimer's Disease: Advances in Etiology, Pathogenesis and Therapeutics. Edited by K. Iqbal, S. S. Sisodia and B. Winblad, 507-513.

12. J. Ghiso, T. Révész, A. Rostagno, **R. Vidal**, G. Plant, and B. Frangione. Familial British dementia. (2001) In: Alzheimer's Disease: Advances in Etiology, Pathogenesis and Therapeutics. Edited by K. Iqbal, S. S. Sisodia and B. Winblad, 487-493.

13. B. Frangione, T. Revesz, **R. Vidal**, J. Holton, T. Lashley, H. Houlden, N. Wood, A. Rostagno, G. Plant and J. Ghiso. Familial cerebral amyloid angiopathy related to stroke and dementia. (2001) *Amyloid.* 1:36-42.

14. J. Ghiso, T. Revesz, J. Holton, A. Rostagno, T. Lashley, H. Houlden, G. Gibb, B. Anderton, T. Bek, M. Bojsen-Moller, N. Wood, **R. Vidal**, H. Braendgaard, G. Plant and B. Frangione. Chromosome 13 dementia syndromes as models of neurodegeneration. (2001) *Amyloid.* 8(4):277-84.

15. **R. Vidal**, M.B. Delisle and B.Ghetti. Neurodegeneration caused by proteins with an aberrant carboxyl-terminus. (2004) *J. Neuropathol. Exp. Neurol.* 63:787-800. (Invited review)

Genbank Submissions:

1) S81436	Homo sapiens transthyretin (thyroid hormone carrier protein/retinol-binding protein). Genomic Mutant, exon 2. Meningocerebrovascular amyloidosis.
2) AF152462	Homo sapiens transmembrane protein BRI mRNA, complete cds and genomic mutant (Familial British dementia or FBD).
3) AF246221	Homo sapiens transmembrane protein BRI genomic mutant (Familial Danish dementia or FDD).
4) AF272043	Homo sapiens transmembrane protein BRI3 mRNA, complete cds.
5) AF272044	Mus musculus transmembrane protein BRI3 mRNA, complete cds.

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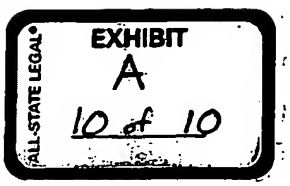
6) AY466472 Human ferritin light polypeptide genomic mutant (Hereditary Ferritinopathy).



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10/684,742

Exhibit B

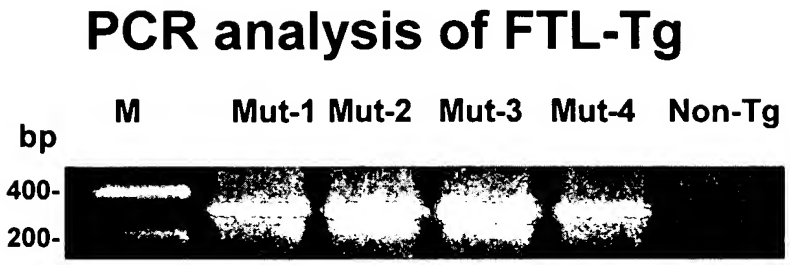
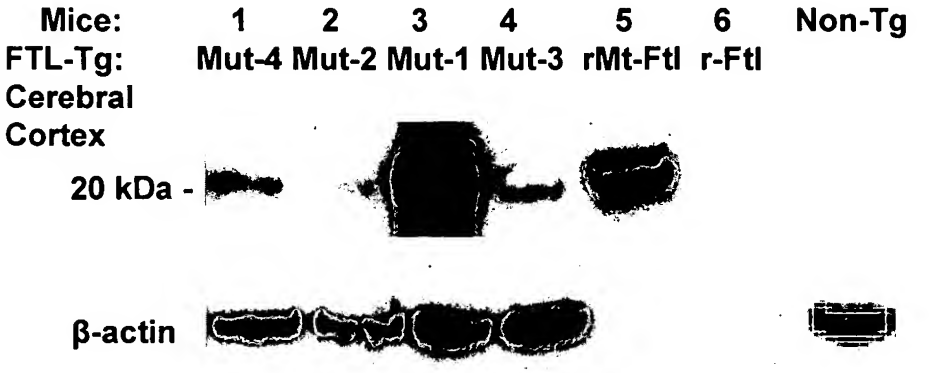
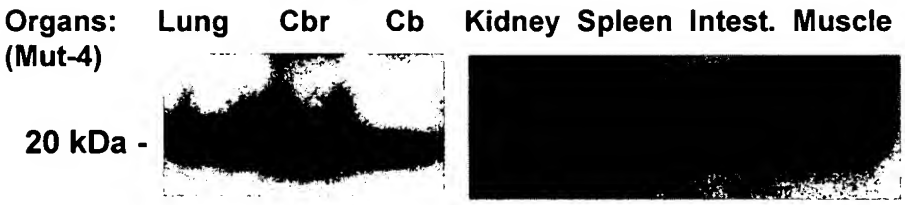


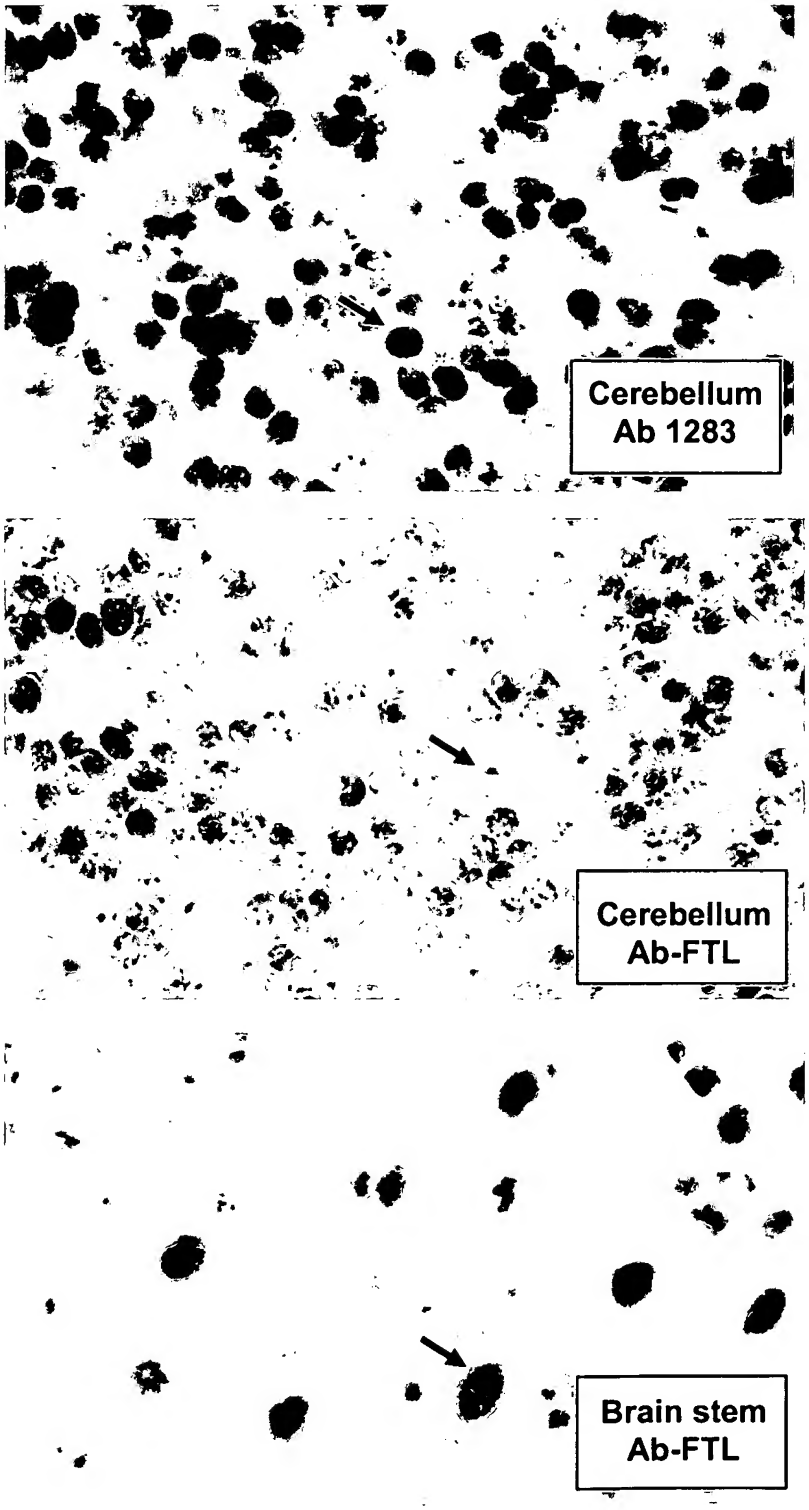
Exhibit C

Expression of Transgene-derived Ferritin





Antibody 1283

Exhibit D

Ferritin Inclusions (4 mo old het Mut-4)